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Dear PHARMAC,

Proposal to move to one funded brand of lamotrigine (Logem)

I am writing to provide feedback on PHARMAC's proposal to reduce the number of funded brands of lamotrigine from three to one.

Medsafe considers that the proposal goes against the international consensus on switching between brands of anti-epileptic medicines. Medsafe also considers that this proposal poses a potential significant safety issue. The international consensus [1] is that even with bioequivalent anti-epileptic medicines, switching could result in the loss of seizure control for any individual using this medicine to control their epilepsy. A single seizure can be extremely detrimental to a patient's life and all measures should be taken to ensure this risk is minimised. Consensus between international organisations and published literature is that any decision to change brands of AEDs should be made between the prescriber and the patient with approval from a specialist.

In this submission Medsafe would also like to comment on statements noted in the minutes of the Neurological Subcommittee of the PTAC meeting held on 11 November 2015, which has been provided as justification for the proposal.

We note that the minutes from the PTAC meeting on 11 November 2015 state that only funding one brand will reduce the potential for inadvertent brand switches. Although there has been funding for three lamotrigine products, the Centre for Adverse Reactions Monitoring (CARM) has only received seven reports of suspected adverse reactions to a brand switch of lamotrigine. The majority of these cases were reported a long time ago when generic brands were first funded. There is no evidence in the current CARM data that this is an ongoing problem. However, as with other brand switches in the past, a small proportion of patients can be expected to suffer from adverse effects when changing brands. I note, however, that three of the seven reports included *convulsion* as an adverse reaction which supports the international consensus. Even a single seizure in an individual previously well controlled is a significant event and risk minimisation measures should be employed where possible.

There is international consensus that patients with epilepsy controlled by antiepileptic medicines (AEDs), including lamotrigine, should not undergo generic substitution without approval from the consulting specialist and under close clinical supervision. From a clinical perspective, the American Academy of Neurology (AAN) has stated that they oppose generic substitution of AEDs for the treatment of epilepsy without the attending physician's approval. To quote one of the authors of this statement:

> *"Epilepsy is unlike other disorders. The marker for success is whether or not you're having seizures and whether or not you're having side effects. So unlike a condition such as hypertension, where, if you make a change in dose you can monitor blood pressure to determine whether it's working or not, with epilepsy you either have an all-or-nothing phenomenon; you're either seizure free or you're not. Having a breakthrough seizure could*

mean a person could lose their driver's license or their job or injure themselves or someone else. This has to be weighed against the potential cost savings of switching to a generic anticonvulsant".

- *George Barkley MD, AAN*

This position is echoed by international regulators, including the Medicines and Healthcare products Regulatory Agency (MHRA), Food and Drug Administration (FDA) and Swedish Medicinal Products Agency. A number of societies and groups with a vested interest in epilepsy and AED usage, including the National Institute for Health and Care Excellence (NICE), the International League Against Epilepsy (ILAE), the Epilepsy Foundation, and the American Epilepsy Society have also recommended avoiding generic substitutions for antiepileptic medicines, including lamotrigine, due to the risk of seizure reoccurrence. Medsafe agrees with the recommendation that patients with controlled epilepsy should not switch between brands of AED (even when bioequivalent) without input and monitoring from specialists.

As noted in the minutes for the Neurological Subcommittee of PTAC meeting on 11 November 2015, the MHRA have provided a risk-based categorisation of AEDs to assist decision making on switching between different brands. The original advice, published in December 2014, categorised lamotrigine as category 2, whereby the need for continued supply of a particular brand should be based on clinical judgement and consultation with the patient/or carer, taking into account factors such as seizure frequency and treatment history. In 2017, the advice was updated to include consideration of patient-related factors. Other medicines in this category include valproate and topiramate, both of which have either the innovator as sole supply or multiple funded brands. Medsafe concurs with this categorisation. Medsafe notes in the 11 November 2015 meeting minutes that the Subcommittee contests this position in relation to lamotrigine. Medsafe agrees with the advice from the MHRA in this situation.

The published literature contains many references supporting Medsafe's advice on switching AEDs. We note that whilst some of the available literature was considered by the Subcommittee, other important studies were not referred to. Additionally, Medsafe considers that some studies noted by the subcommittee were either not relevant to lamotrigine and/or the current proposal by PHARMAC.

A systematic review by Desmarais et al in 2011 noted that studies have reported higher switch-back rates following generic substitution of AEDs than substitution of other commonly prescribed medicines. Specifically, a switch from Lamictal to generic lamotrigine, has been associated with increases in required dose, increased number of co-prescribed AEDs, more frequent outpatient visits and longer hospitalisations. Although seizure reoccurrence was not a measured outcome, the authors of these studies suspect this to be a factor in the observed increase in medical-service utilisation and longer hospital stays [2].

The Subcommittee considered a systematic review by Kesselheim et al, however none of the studies included lamotrigine. Additionally, the results of the review stated that no randomised controlled trials found that the brand-name AED was superior or inferior to the generic product in controlling seizures. Medsafe has already established the non-inferiority of generic products through its generic medicine approval process. Therefore, the RCTs in this study are of limited relevance to the current proposal as they do not evaluate the action of substitution, only the efficacy of generic products. However, the observational studies of patients with epilepsy who were switched from brand to generic products identified changes in health-service utilisation that the authors concluded may suggest less than adequate seizure control with the generic product [3]. Therefore, this study supports the notion that switching patients from one brand of AED to another may be detrimental to the seizure control for patients taking lamotrigine for epilepsy.

The Subcommittee also considered a systematic review by Yamada et al. The authors of this review concluded that retrospective studies suggested issues with generic substitution of AEDs, while prospective studies suggested it can be safe. The authors call for healthcare professional diligence to minimise the risk of serious treatment failure consequences [4].

Thank you for the opportunity to provide feedback on this proposal. If you would like to discuss this further, please do not hesitate to contact me.

Yours sincerely,

Chris James
Group Manager
Medsafe

1. Atif M, Azeem M and Sarwar MR. 2016. Potential problems and recommendations regarding substitution of generic antiepileptic drugs: a systematic review of literature. *SpringerPlus* 5(1): 182.

2. Desmarais JE, Beauclair L and Margolese HC. 2011. Switching from brand-name to generic psychotropic medications: a literature review. *CNS neuroscience & therapeutics* 17(6): 750-760.

3. Kesselheim AS, Stedman MR, Bubrick EJ, et al. 2010. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs. *Drugs* 70(5): 605-621.

4. Yamada M and Welty TE. 2011. Generic substitution of antiepileptic drugs: a systematic review of prospective and retrospective studies. *Annals of Pharmacotherapy* 45(11): 1406-1415.

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21 November 2018

Sarah Fitt
Chief Executive PHARMAC
by email: sarah.fitt@pharmac.govt.nz

Dear Sarah

Clarification of Medsafe's position re potential funding changes for lamotrigine

Thank you for providing Medsafe with the opportunity to clarify our earlier submission to PHARMACs consultation on lamotrigine funding. We note your decision to seek further advice from Medsafe and would also like to clarify our interpretation of the paper stated to be the best evidence of successful switching of lamotrigine.[1]

Medsafe has some concerns regarding this paper.

One of the stated aims of the study is to assess the use of national administrative databases to evaluate health outcomes and potential costs or savings to generic reference pricing in New Zealand. However no validation of the method appears to be reported in the paper. Some of the limitations are discussed but this is not a method validation. The National Minimum Data Set (NMDS) may not be a reliable source of epilepsy-related outcomes, the authors did not appear to explore whether patients with epilepsy who experience a seizure are captured in this dataset.

From a pharmacovigilance perspective the paper is not meaningful, firstly because we do not know that the methodology could detect any difference. Secondly because the power of the study to exclude a level of harm was not discussed. As the outcome was negative from our perspective we would like to know at what frequency level this might represent reassurance. In other words does the study exclude a frequency of harm of 1 in 10 or closer to 1 in 1000? This figure will be relevant to determining the likely cost benefit to the health care system.

In addition the results of this analysis are unlikely to be predictive of events that would occur after a switch to sole supply. In a similar analysis for venlafaxine switching it was also concluded there was no change in health outcomes.[2] However, the current reports

[1] Lessing C, Ashton T, Davis P (2014) 'The impact on health outcomes and healthcare utilisation of switching to generic medicines consequent to reference pricing: The case of lamotrigine in New Zealand' Appl. Health Econ. Health Policy 12: 537-546

[2] Lessing C, Ashton T, Davis P (2015) 'AN evaluation of health service impacts consequent to switching from brand to generic venlafaxine in New Zealand under conditions of price neutrality' Value in Health 18 646-654

to the Centre for Adverse Reactions Monitoring (CARM) regarding venlafaxine suggest that there may have been increased utilisation of healthcare services.

Finally we note that description of bioequivalence in the introduction to this paper is incorrect.

We note during the discussion in our meeting that studies showing adverse effects of switching brands of lamotrigine were dismissed because they were sponsored by pharmaceutical companies. This position is inconsistent with PHARMACs acceptance of pharmaceutical company sponsored biostudies for funding generic medicines. The studies may not have been reliable but that should be concluded after careful analysis, not dismissed based on the funding source for the study alone.

Medsafe notes that the current proposal to change the funding for lamotrigine is based on an analysis that was conducted three years ago. We suggest that a review of the scientific literature since then may reveal additional useful information. For example the results of the EQUIGEN trial published in 2017 concluded that lamotrigine products were bioequivalent in patients with epilepsy.[3] Whereas bioequivalence studies are normally performed in healthy volunteers.

The UK epilepsy society has published a survey on patient experiences of switching anti-epileptics which provides further insight into the problems that patients might experience with a change in funding. Medsafe notes that switching lamotrigine was cited most often by patients in this survey as leading to negative effects. We know that negative perceptions are a major cause of 'brand switch' reactions. If similar perceptions are formed around a lamotrigine we expect to receive a significant number of adverse reaction reports. Each time these events occur patient and healthcare professional trust in the health system is reduced.

Should PHARMAC decide to go ahead with a sole supply tender for lamotrigine Medsafe recommends that affected patients are first reviewed by their GPs. The switch should not occur when the patient reaches the pharmacy without prior counselling by the GP. GPs should also refer the most vulnerable patients for specialist intervention to oversee and monitor the switch.

For patients with epilepsy the most vulnerable people are considered to be those who are seizure free since the impact of a seizure would be profound, and those with labile seizures since any variability could lead to loss of control. We would expect that switching in these patients would need to be managed by a specialist. Therefore the usual time period for switching may need to be extended.

Patients with epilepsy may also have memory problems or learning difficulties therefore a patient leaflet will be needed to help explain in changes in the tablet or dose. This leaflet will need to be readable and understandable by this group of people. Leaflets should be distributed by both GPs, specialists and pharmacists. All patients should be actively followed up to check that they are coping well with the change.

[3] Berg M, Welty T, Gidal B et al (2017) "Bioequivalence between generic and branded lamotrigine in people with epilepsy The EQUIGEN randomized clinical trial' JAMA Neurology 74:919-926

For patients taking lamotrigine for other indications switching is generally considered to be less problematic, however this group of patients generally finds change very difficult and will need at least GP level support and monitoring.

Healthcare professionals and patients should be reminded of the symptoms which may indicate a risk of reduced bioavailability and those of increased bioavailability so that urgent review can occur. There appears to be a number of case reports in the literature which may provide information in the absence of advice from PHARMACs event advisory groups. Of particular concern to Medsafe would be a breakthrough seizure, induction of hypersensitivity, QT prolongation and suicidality.

Medsafe notes that these actions to mitigate harm occurring to patients have the potential to significantly increase the cost of healthcare for the patient. PHARMAC should consider ways to mitigate these costs and to actively consider how health equity issues will be addressed. In addition PHARMAC should ensure that an alternative funding mechanism is made more accessible for patients who need to switch back to their original brand.

Yours sincerely

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